UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' REPLY BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT FENGTIAN XUE, PH.D.

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PRELIMINARY STATEMENT

ZHP's opposition describes Dr. Xue as a "rebuttal" expert as if that excuses an expert from complying with *Daubert*. The "rebuttal expert" narrative does not shield an expert from the requirements that an expert be both qualified and employ a reliable methodology in order to offer opinions. ZHP further attempts to recast Dr. Xue's opinions to fit the case, and mischaracterize Plaintiffs' arguments in an effort to save Dr. Xue's opinions. This transparent attempt to restate the record should be rejected.

As explained in Plaintiffs' opening brief, Dr. Xue failed to apply the proper, relevant standard to determine whether ZHP conducted the necessary risk assessment in developing and manufacturing its valsartan, rendering his opinion unfit for this case. Importantly, this inadequacy also prevents his opinions from matching up with and answering those of Plaintiffs' experts, who did apply the proper, relevant standard. Moreover, Dr. Xue's report is not written in rebuttal to Plaintiffs' experts' opinions. Dr. Xue confirmed his report sought to prove three points:

> (1) ZHP performed reasonable and appropriate scientific risk assessments regarding the relevant manufacturing processes it used to create its Valsartan API given the information reasonably available in the field of organic chemistry at the time;
>
> (2) ZHP performed reasonable and appropriate scientific testing of its Valsartan API for potential impurities during the time that its Valsartan API was available on the market; and
>
> (3) ZHP did not know, and could not have been reasonably expected to know, that the manufacturing processes for its Valsartan API could result in the formation of NDMA or NDEA until it was alerted to the presence of these impurities in its Valsartan API by customer Novartis in 2018.

(Xue R. 3 (Ex. 2);[1] Xue Dep. 28:2-5, 30:11-13, 31:13-14, 46:8-10, 51:1-2, 52:2-3, 53:21-22, 65:8-14, 395:16-18 (Ex. 1)). These are affirmative opinions, and are untethered to Plaintiffs' experts.

To the extent he acknowledges considering potential problems with ZHP's risk assessment, Dr. Xue parrots his review of the material and then claims he would not have bothered to search for it, would not have found it, or would not have read it thoroughly enough to find the relevant information. Even worse, during his deposition, Dr. Xue admitted he did not consider whether ZHP should have recognized that dimethylformamide and triethylamine were well known to contain the impurities dimethylamine and diethylamine, and those substances along with triethylamine can be nitrosated by sodium nitrite/nitrous acid to form NDMA and NDEA. In order to plaster over this hole in his methodology, ZHP claims Plaintiffs' experts never discussed this issue, which is unavailing since this **was** considered by Plaintiffs' experts. And Dr. Xue cannot support his three opinions because he did not consider these pathways to the contamination.

Dr. Xue's "see no evil" methodology is exemplified by his unsound description of the July 27, 2017 email, which stated that valsartan becomes contaminated with NDMA when quenched with sodium nitrite. Dr. Xue declares that the email has a meaning contrary to that provided by ZHP's 30(b)(6) witnesses, ZHP, and the Plaintiffs. Dr. Xue does not provide his alternate "translation" of the email. He simply says no, it does not say what everyone else has said it does—attempting to create new facts. Dr. Xue's opinions are unsound and should be precluded.

[1] Unless otherwise noted, exhibits are attached to the initial certification in support of this motion, with the exception exhibits 27 through 29, which are attached to Adam M. Slater's certification in support of this reply.

ARGUMENT

I.
DR. XUE'S OPINIONS DO NOT FIT THIS CASE OR REBUT THE OPINIONS OF PLAINTIFFS' EXPERTS

"Rule 702 requires that the expert's testimony must assist the trier of fact." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 742-43 (3d Cir. 1994). The Third Circuit has explained that "admissibility [consequently] depends in part on 'the proffered connection between the scientific research or test result to be presented and particular disputed factual issues in the case.'" *Id.* at 743 (quoting *U.S. v. Downing*, 753 F.2d 1224 (3d Cir. 1985)). Importantly, "scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes." *Id.* "Thus, even if an expert's proposed testimony constitutes scientific knowledge, his or her testimony will be excluded if it is not scientific knowledge **for purposes of the case**." *Id.* (emphasis added).

Dr. Xue admitted that he could not opine on the fundamental question he was ostensibly brought in to address, which was the availability of the relevant scientific information to ZHP during the relevant time period, and what the ZHP chemists should have found: "**Yeah, I cannot speculate what result if I don't do that. I don't even know if I do something today I didn't do yesterday what I would have got. So I cannot speculate**." (Xue Dep. 234:12-235:2). Dr. Xue could not even "comment" on the extent of the "scientific analysis that the people working at ZHP were required to conduct based on the regulations and the standard operating procedures that applied to them." (*Id.* at 176:18-22; 177:4-6). He conceded that he was not qualified to offer any testimony as to "how extensive the risk assessment was supposed to be," stating "I'm not qualified to comment on those." (*Id.* 288:23-290:3). As a result, Dr. Xue was completely unaware, based on the FDA guidance adopted per ZHP's own regulatory filings, that **ZHP was "required to make every feasible technical effort to prevent the formation of genotoxic or carcinogenic**

compounds during the manufacture of valsartan." (*Id.* at 214:17-20; 215:1-5; FDA, Guidance for Industry, *Genotoxic ad Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Dec. 2008) (Ex. 10); HUAHIA-US00007898 (stating, "FDA draft guideline "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches' is applicable to the applications for existing active substances") (Ex. 11); PRINSTON00080018 (same) (Ex. 12)).[2] Unaware of the required scope of the scientific evaluation, he was never in a position to measure ZHP's conduct against that or any other relevant or reliable standard—and thus only applied his own personal standard, which is irrelevant to this case as well as Plaintiffs' experts' opinions, which applied the relevant objective standard.

Dr. Xue's foundation was so weak that Dr. Xue could not opine on "whether or not ZHP was required to ensure that there were no genotoxic impurities in the valsartan it was manufacturing." (Xue Dep. Tr. 162:5-8, 16-17). His failure to address this obviously central question at any level, much less to know that this was required per an explicit ZHP internal SOP titled Guideline for Genotoxic Impurity Evaluation, is inexplicable.[3] And since he did not address the organic chemistry aspects of this fundamental point of the risk assessment, and he did not measure the evidence to determine whether or not this could or should have been accomplished, his opinion cannot fit the case. *Paoli*, 35 F.3d at 742-43.

In an effort to skip over these large gaps, ZHP cites a series of inapposite cases holding that experts in an industry can opine on various subparts of that industry. (Defs.' Br. 15). However, Dr. Xue is not an expert in developing manufacturing processes for human drugs or manufacturing

[2] ZHP argues that Dr. Xue should be allowed to testify regarding what was "generally known in the field of chemistry a decade ago" (Defs.' Br. 10), but that is not the relevant standard in this case. The question is what the chemists at ZHP should have considered regarding the manufacture of valsartan with their own proprietary processes.

[3] (Peng Dong 3/29/2021 Dep. Tr. 33:9-62:16 (Ex. 13)).

drugs in general, and his failure to couch his opinions within the context of the applicable standards in reaching his opinions distinguishes this situation and this case from those relied on by Defendants.

II.
DR. XUE DID NOT LIMIT HIS OPINIONS TO "REBUTTING" PLAINTIFFS' EXPERTS

ZHP attempts to recast Dr. Xue's report as "rebutting" its narrow interpretation of Plaintiffs' experts' own reports, but a plain reading of Dr. Xue's report and testimony does not support this tactic.[4] (Xue R. 3; Xue Dep. 28:2-5, 30:11-13, 31:13-14, 46:8-10, 51:1-2, 52:2-3, 53:21-22, 65:8-14, 395:16-18). Dr. Xue's three opinions are not directed at the discrete issues that ZHP mistakenly contends Plaintiffs' experts addressed in their reports. Instead, they are ZHP's general defense in this case.

In order to support these general statements, Dr. Xue would need to consider ALL the ways ZHP's valsartan manufacturing processes could have created NDMA and NDEA. This is why, despite ZHP's insistence to the contrary, Dr. Xue needed to review and seriously consider ZHP's deviation investigation reports, which established the root cause of the NDMA and NDMA contamination from a theoretical perspective and then confirmed that perspective using actual lab experiments. (*See* PRINSTON00075797 (Ex. 4); PRINSTON0076100 (Ex. 5)). Dr. Xue was

[4] ZHP contends that Dr. Hecht never opined that DMF and TEA could contain dimethylamine and diethylamine, but his reports and deposition show otherwise. (*See, e.g.*, Dr. Hecht 7/6/21 R. 20-21 (Ex. 24); Dr. Hecht 10/31/22 Report, at 2-3 (Ex. 26); Dr. Hecht 1/13/23 Dep. Tr. 46:5-7, 52:25-53:5, 54:4-9, 54:25-55:3, 56:3-5, 57:19-23 (Ex. 27)). Dr. Xue wrote a whole supplemental report to address Dr. Najafi's deposition, which occurred after Dr. Hecht's deposition, but ZHP opted not to have him address Dr. Hecht's opinions on dimethylamine and diethylamine contaminating DMF and TEA. That was their decision. They cannot claim prejudice at this late juncture. *See nCube Corp. v. SeaChange Int'l, Inc.*, 809 F. Supp. 2d 337, 347 (D. Del. 2011) (focusing on "whether the objecting party had notice of the subject matter of the testimony based on the contents of the report and elaborations made during any deposition testimony.").

unable to apply a reliable methodology without factoring in and discussing these important root cause analyses in ZHP's deviation investigation reports.

III.
DR. XUE DID NOT APPLY A RELIABLE METHODOLOGY IN REACHING HIS OPINIONS

ZHP cites a single Third Circuit case for the idea that "rebuttal" experts somehow face a lower standard of admissibility for their opinions under *Daubert*. That is obviously untrue.

Holbrook v. Lykes Bros. S.S. Co. focused on whether the defense expert had offered his opinion with the requisite "certainty" when the defendant did not bear the burden of proof on the issue at hand. 80 F.3d 777, 785-86 (3d Cir. 1996). The Court held that the expert had "testified on this issue to a reasonable degree of medical certainty," explaining "[a]lthough that testimony would have been insufficient to prove that radiation exposure caused the cancer, a burden which the defense did not bear, it was sufficiently certain and could help the jury to evaluate testimony by plaintiff's experts that asbestos exposure caused the cancer, an issue on which plaintiff bore the burden of proof." *Id.* at 786. Plaintiffs' motion does not attack Dr. Xue's opinions based on his level of certainty, as he states in his report that he holds his opinions to a reasonable degree of scientific certainty, so *Holbrook* is irrelevant to Plaintiffs' arguments concerning the reliability of Dr. Xue's methodology.

ZHP's nonbinding trial court cases are equally irrelevant to Plaintiffs' attacks on Dr. Xue's methodology. His opinions are subject to the same requirements as any other expert. *See, e.g.*, Rule 702 (making no distinction between which party proffers the expert); *Montgomery County v. Microvote Corp.*, 320 F.3d 440, 447-49 (3d Cir. 2003) (excluding the defense expert after reciting the standard *Daubert* analysis, explaining "the data underlying [the defense expert's] opinion was so unreliable that no reasonable expert could base an opinion on it"); *United States v. Ancient Coin*

Collectors Guild, 899 F.3d 295, 318-19 (2018) (applying the standard *Daubert* analysis and holding: "The district court's application of the particularization requirement thus ensured that the Guild's rebuttal expert evidence 'fit' the questions presented in the forfeiture proceedings"); *Decker v. GE Healthcare Inc.*, 770 F.3d 378, 394 (6th Cir. 2014) (denying the defendants' appeal that "the district court violated *Daubert* because it excluded key rebuttal evidence proffered by [its] experts").

Plaintiffs' initial brief demonstrates that Dr. Xue repeatedly disregarded documents showing that basic research into the chemistry of ZHP's valsartan manufacturing processes would have at the very least raised the potential for creating NDMA and NDEA. Unable to dispute the existence of this literature and other documentation, Dr. Xue testified that in his lab work experimenting to discover new drug substances, he would not have searched for the relevant materials, would not have found the relevant materials, or would not have read the relevant materials closely enough to see their relevance to this case. This subjective "see no evil" approach is not a reliable methodology, and is totally unhelpful. *See In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018) (quoting *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004)); *see also In re Zoloft Products Liability Litigation,* 26 F. Supp. 3d 449, 460-61 (E.D. Pa. 2014) (citing *In re Rezulin Products Liability Litigation,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) (**"[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable."**)).

Even worse, Dr. Xue refused to offer an opinion as to whether, if "the chemists at ZHP knew that DMA could be introduced to the zinc chloride process as an impurity of the DMF, they needed to take that into account when they did a risk assessment for the process." (Xue Dep.

156:3-158:5) ("I didn't go ahead to address that")). Defense counsel actually confirmed that it was "[o]utside the scope of his expertise" to answer whether, "[i]f [ZHP] knew that the DMF could introduce DMA to the zinc chloride process, either as an impurity or as a degradation product, then under those circumstances, they would have been required to take the prudent step of testing to see if NDMA was being formed." (*Id.* at 296:13-21). Dr. Xue similarly testified that he could not "judge whether any impurity, including diethylamine was part of the TEA they bought." (*Id.* at 208:9-14). This contradicts his practice outside of litigation, where he testified that he routinely reviews certificates of analysis and other documentation to determine the impurities of the materials he uses. (*Id.* at 127:13-17). After being shown certificates of analysis and other documents showing DMF and TEA contain impurities necessary for the formation of NDMA and NDEA, Dr. Xue backtracked and said, "**Well, I cannot speculate for any other people than myself. I told you I do that**."[5] (*Id.* at 134:18-24). In other words, he is not able to offer an opinion that "fits" the case. Plaintiffs' opening brief is replete with examples of this type of subjective, confusing, contradictory, and self-serving testimony.[6] This is **not** attributable to Dr. Xue's country

[5] ZHP seems to think that Dr. Xue properly disregarded all the evidence that DMF and TEA contain dimethylamine and diethylamine as impurities because that evidence "does not establish that those contaminants were in fact present in the DMF [or TEA] that ZHP purchased." (Defs.' Br. 23). First, that is not true, as the certificates of analysis are for manufacturers that ZHP's deviation investigation report shows supplied the DMF and TEA used here. (*Compare* Ex. 15, *with* PRINSTON00075959; *compare* Ex. 17, *with* PRINSTON00075957). Second, Plaintiffs do not even need to show ZHP used the same suppliers, as the main point is that DMF and TEA routinely contain these impurities, so ZHP was on notice that these impurities could be present in their process and should have realized they could react with sodium nitrite to form NDMA and NDEA, requiring, at the very least, ZHP to test for NDMA and NDEA, after which the contaminants would have been detected and the manufacturing processes discarded as violating cGMP, just as the FDA mandated in 2018. ZHP's effort to complicate a straightforward issue has failed.

[6] ZHP contends that "Dr. Xue did not 'subjectively' disregard the Sun article in opining that reasonable chemists would not have known that ZHP's processes were capable of resulting in NDMA/NDEA." (Defs.' Br. 25). But Dr. Xue's deposition testimony is clear: "Things like this, as I said, I don't want to be, you know, disrespectful for other people's work, but I will say **I will just skip. I won't take it too seriously. That's me**." (Xue Dep Tr. 244:23-245:23). Plaintiffs' brief

of origin or proficiency with the English language, as ZHP cynically accuses Plaintiffs of arguing. (Defs.' Br. 2-3). Instead, it is entirely attributable to Dr. Xue's results-oriented methodology and his failure to account for all the evidence directly relevant to his three overarching opinions that ZHP did nothing wrong.

Dr. Xue's bald assertion that the July 27, 2017 email does not say what every other person in this case has said it says is another flagrant example of his impermissible "see no evil" methodology. For the sake of brevity and clarity, Plaintiffs will focus on the most important sentence from the email, which has been confirmed numerous times:

- "Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; **it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic.**" (**Pls.' Translation** of ZHP00190573 (emphasis added) (Ex. 20)).
- Through the secondary mass spectrometry analysis, it can be inferred that the additional NO substituent is in the cyclic compound fragment part, and **it is** probably that it is the N-NO compound, **similar to the N nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite, its**

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has additional quotations of Dr. Xue making the applying the same subjective to disregard Sun and every other piece of literature or other article shown to him. Moreover, ZHP's deviation investigation report cited the Sun article (from 2010) for the proposition that "TEA could react with nitrous acid directly to form NDEA without proceeding via the intermediary of DEA." (PRINSTON0076108 (Ex. 5)). This makes it even clearer why Dr. Xue needed to carefully read and analyze ZHP's deviation investigation reports to then exclude any reasonable basis for anticipating the numerous ways the manufacturing processes could create NDMA and NDEA. Obviously, ZHP never had him do this because it is an impossible exercise, as shown by the Sun article and many others.

structure is very toxic." (**ZHP's Translation** of ZHP00190573 (emphasis added) (Ex. 21)).

- "Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; **it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic**." (**30(b)(6) Corporate Representative Min Li** 4/20/2021 Dep. Tr. 87:19-88:7 (Ex. 19)).

ZHP seems to insinuate that Min Li was shown Plaintiffs' translation when he confirmed it during his deposition (Defs.' Br. 27-28 n.7), but the transcript is clear that Plaintiffs "put up" ZHP 295, which is **the original Chinese document**, and ZHP's former counsel even asked "Adam, do you have an English language version of the document," and Plaintiffs then put their translation (ZHP 296) in the exhibit share link for defense counsel. (*Id.* at 82:11-12, 83:18-24). ZHP's current counsel even agreed with the above translations and confirmed it with Jucai Ge in May 2022:

> Q. The sentence that Mr. Slater read you -- and you can pull it up if you want to refresh your recollection -- says that **what was occurring in irbesartan was similar to the NDMA that occurs in valsartan when quenched with sodium nitrite**.
>
> **Do you recall that sentence?**
>
> A. As for that sentence -- hold on. Let me read it.
>
> **I recall it. I see it now.**

(Jucai Ge 5/27/2022 Dep. Tr. 249:16-250:1 (emphasis added) (Ex. 28)). Before providing this confirmatory testimony, Jucai Ge actually spoke with Jinsheng Lin ex parte herself. (Jucai Ge 5/26/2022 Dep. Tr. 14:9-11 (Ex. 29)).

Dr. Xue's report attempts to change the undisputed record of this case based on his own *ipse dixit* and ex parte discussions with Jucai Ge and Jinsheng Lin. He does not even provide his own translation of the email, so the only translations in the record are the ones he is refusing to contend with. It is difficult to think of testimony that would be more confusing and less helpful to a jury than allowing a subject matter expert to contradict every other translation of a critical document. This type of conclusory, just-trust-me testimony is emblematic of Dr. Xue's approach to the entire case. The Court should consequently preclude his opinions from reaching a jury.

CONCLUSION

For the foregoing reasons, Dr. Xue failed to adopt or apply a reliable methodology, and he should therefore be precluded from offering his proffered opinions.

Respectfully,

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Dated: April 25, 2023

CERTIFICATE OF SERVICE

I hereby certify that on April 25, 2023, I electronically filed this brief and my supporting certification with the Clerk of the Court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL. In addition, I hereby certify that an unredacted copy of my supporting certification will be served contemporaneous to filing via email on the Court, Special Master, and the Defense Executive Committee at DECValsartan@btlaw.com, with the exception of the unredacted exhibits, which will be sent to the Court on a thumb drive via FedEx and to the Defense Executive Committee via a Dropbox link.

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Dated: April 25, 2023